

**Figure 1. N-linked Glycoprotein Structures.**

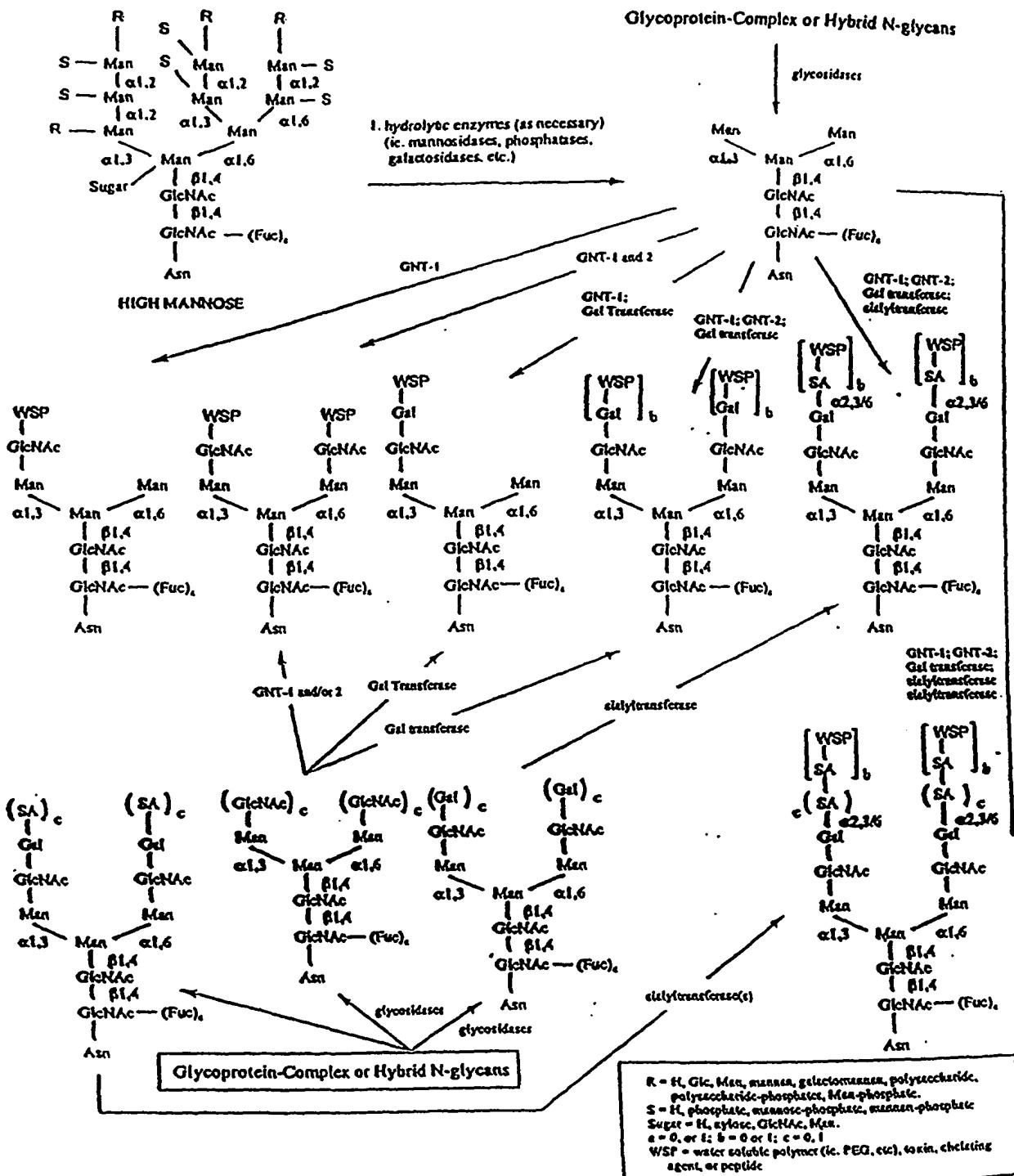


FIG. 1

**Scheme 2.**

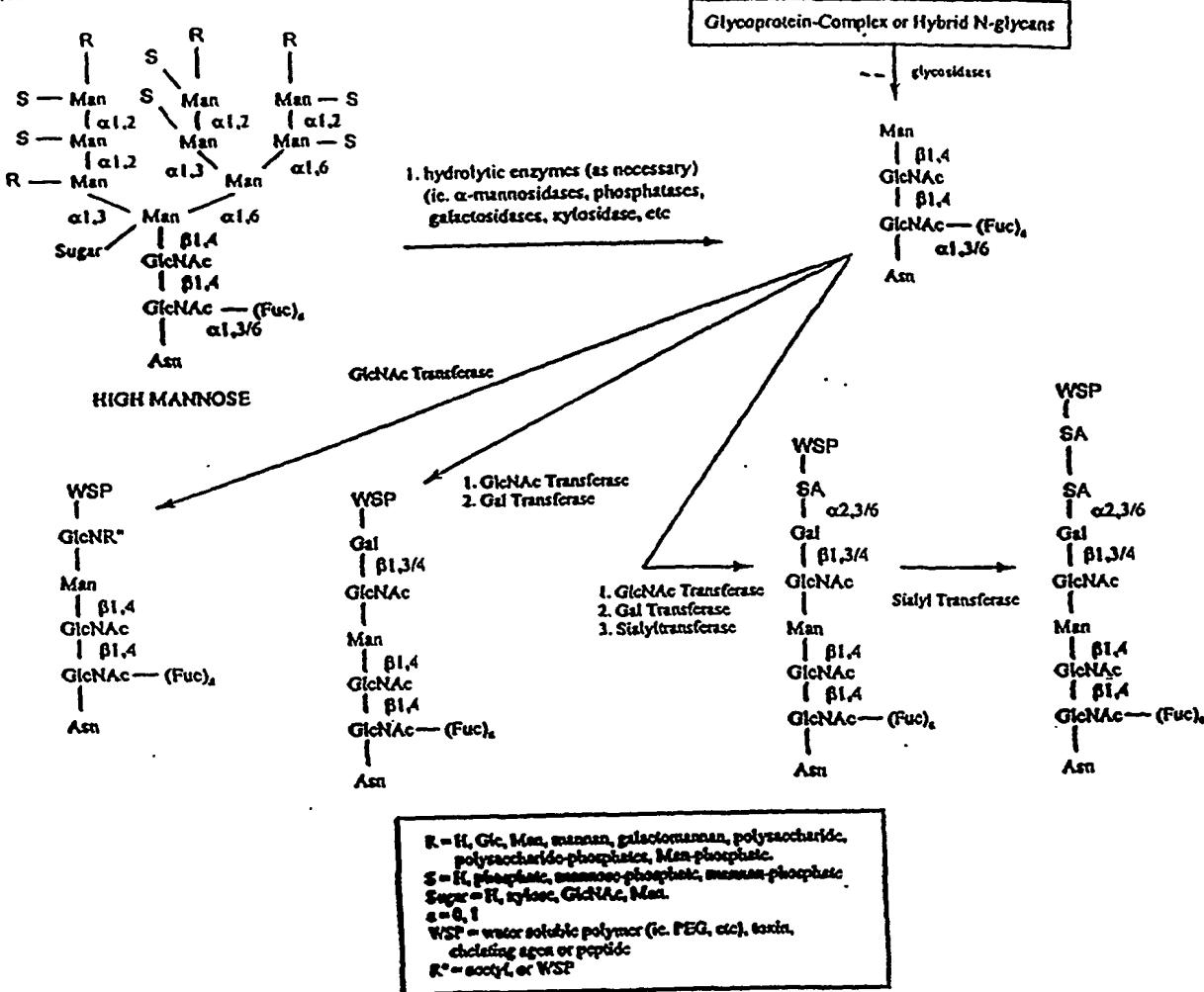


FIG. 2

Scheme 3.

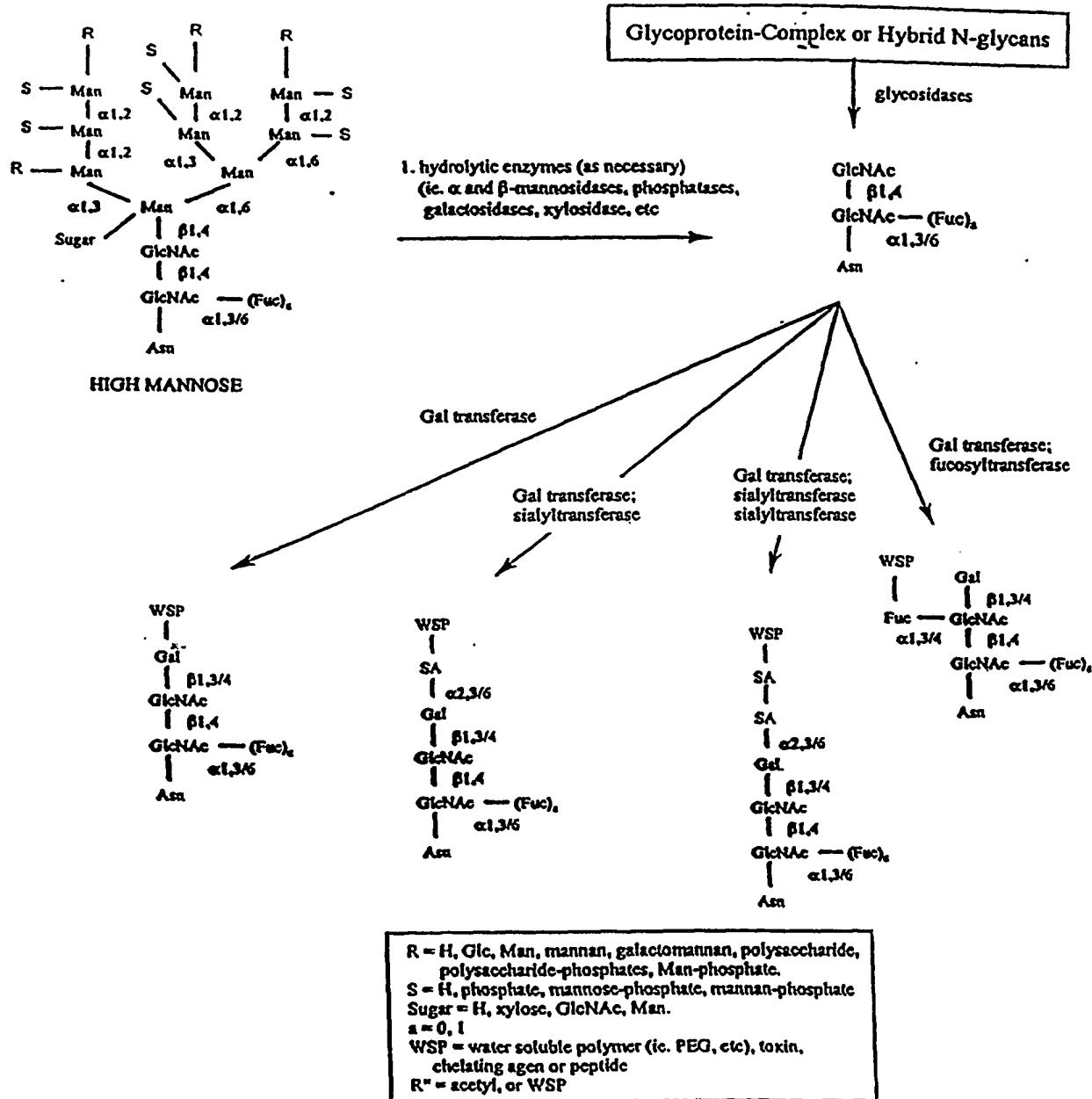


FIG. 3

Scheme 4.

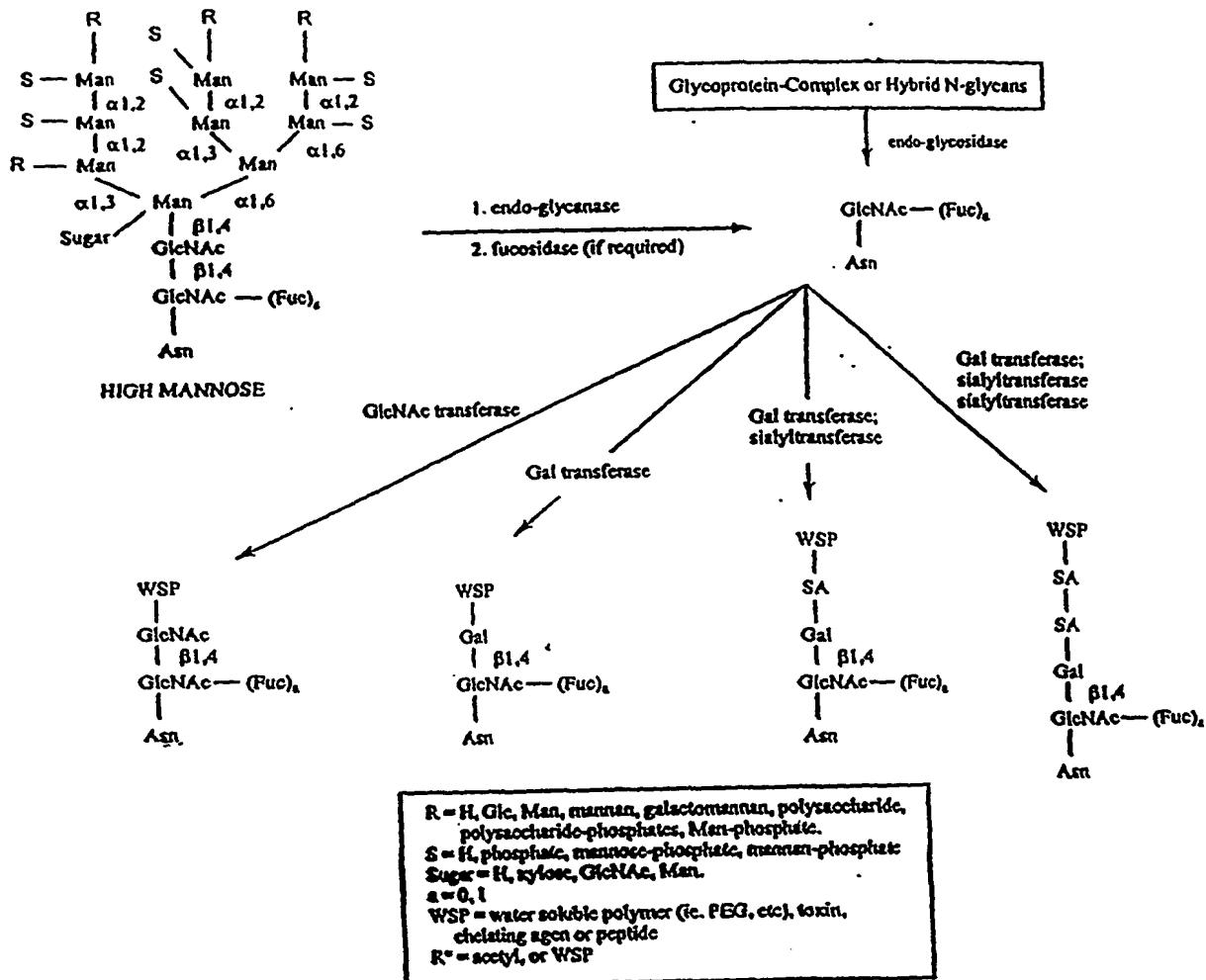


FIG. 4

Figure 5. N-linked Glycoprotein Structures.

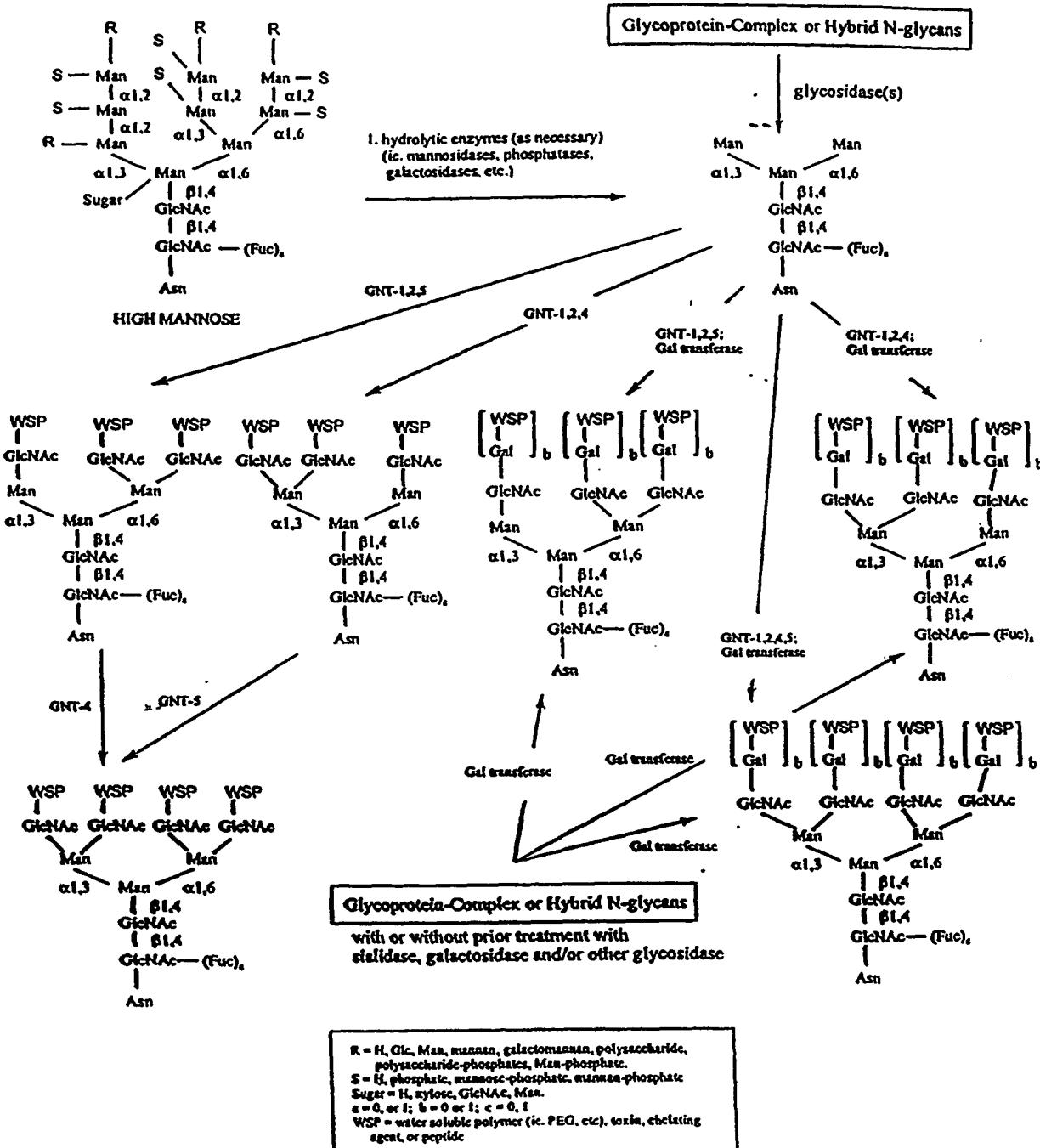


FIG. 5

Figure 6. N-linked Glycoprotein Structures.

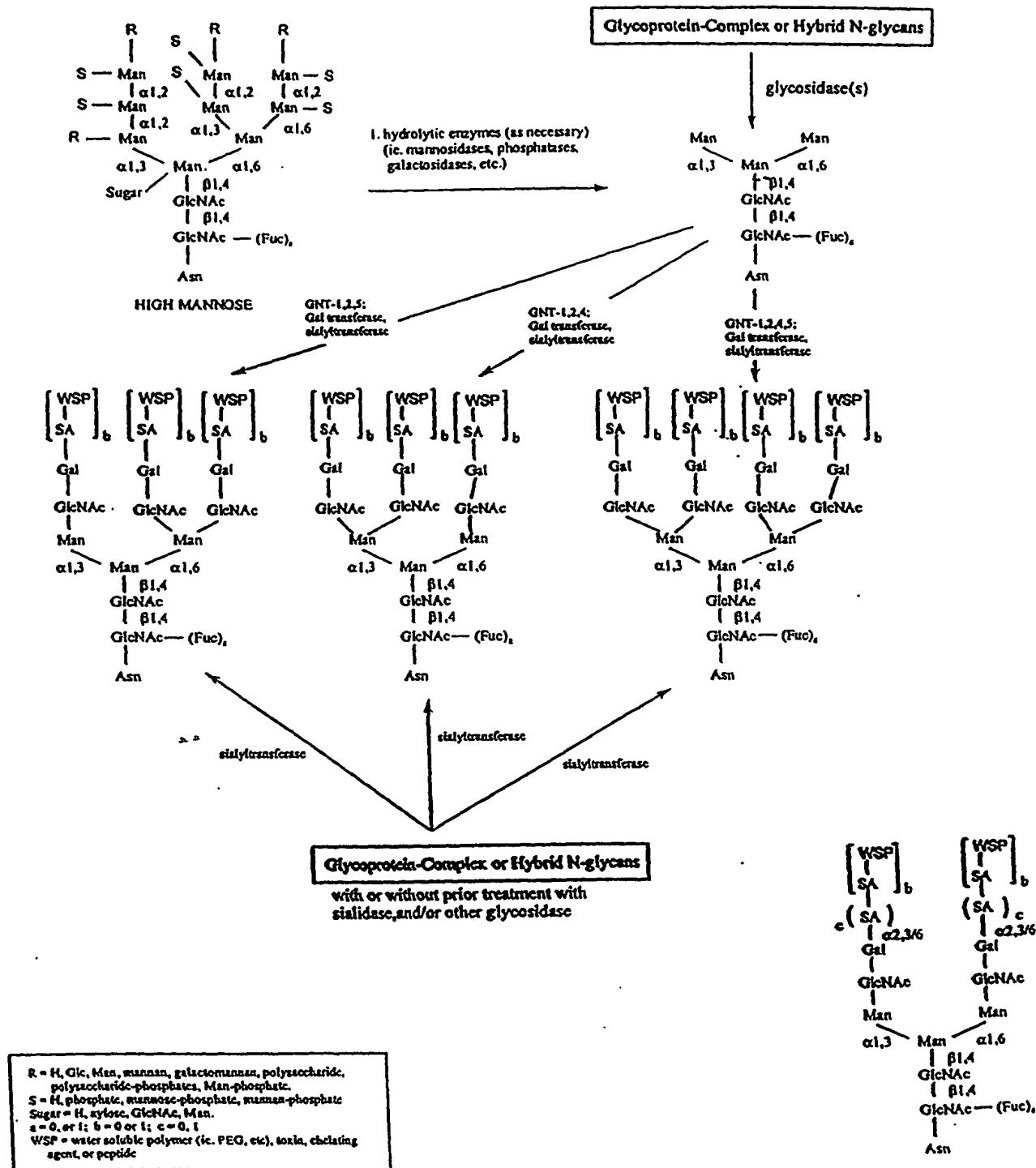


FIG. 6

Figure 7. N-linked Glycoprotein Structures.

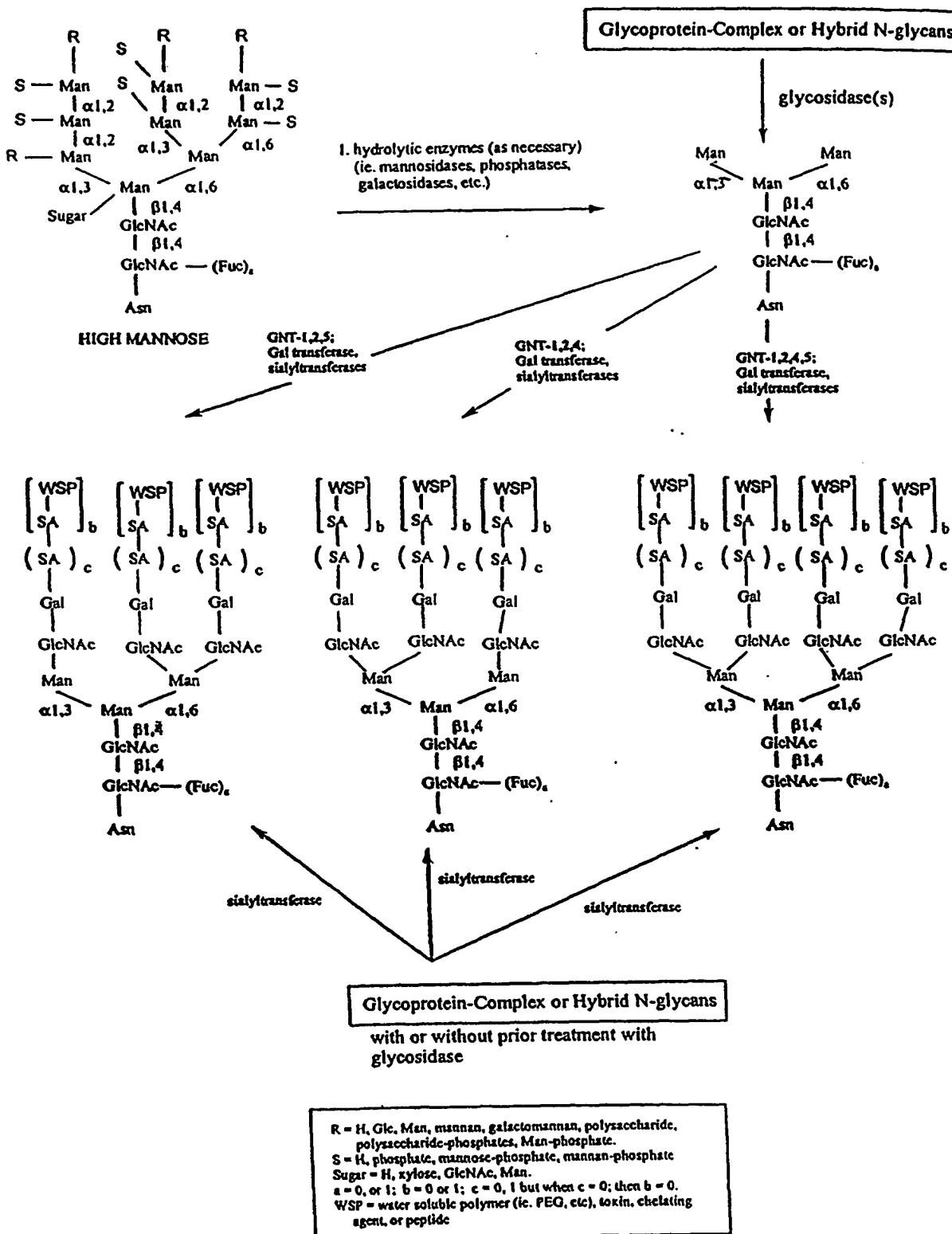


FIG. 7

Scheme 8.

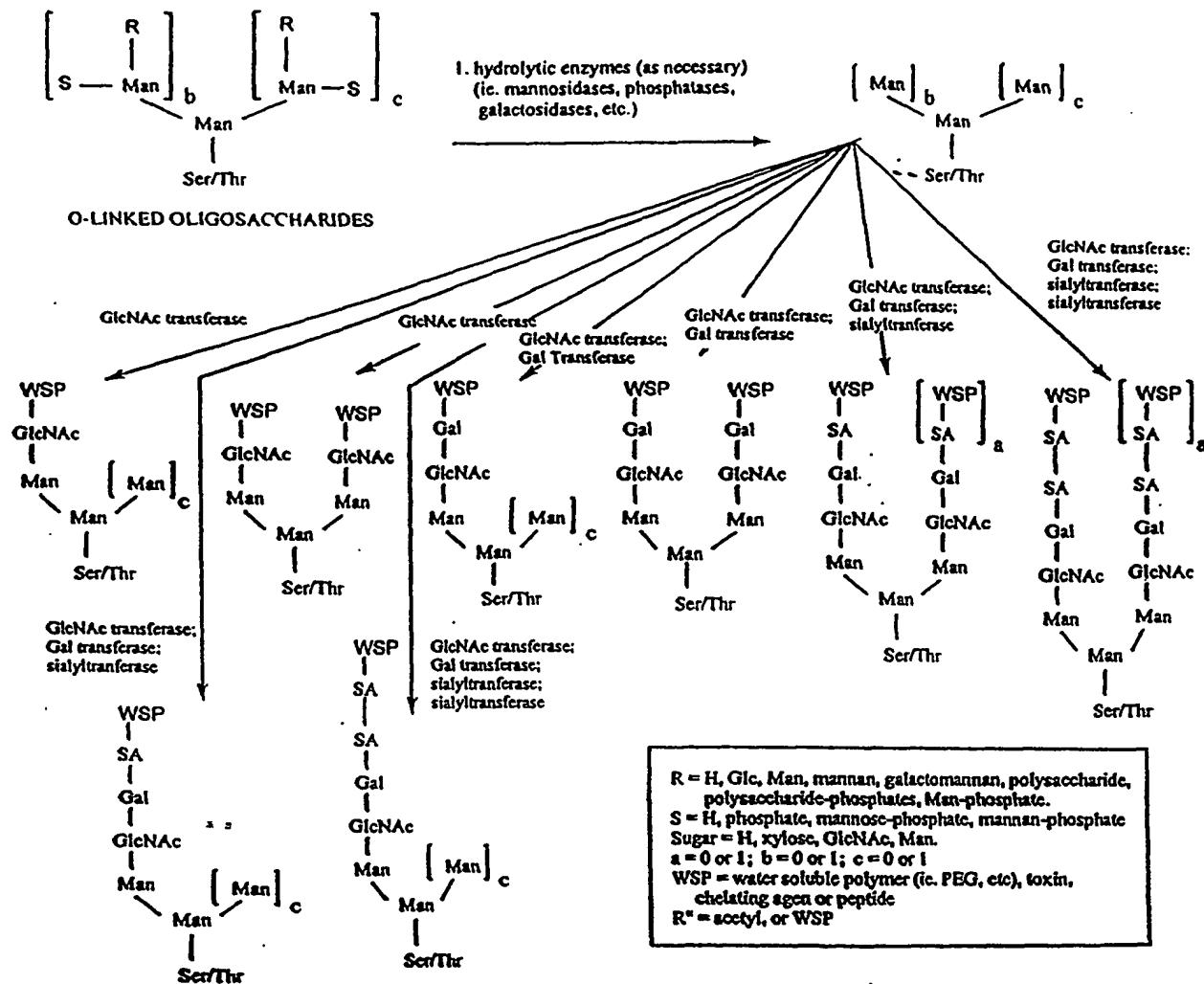


FIG. 8

**Scheme 9.**

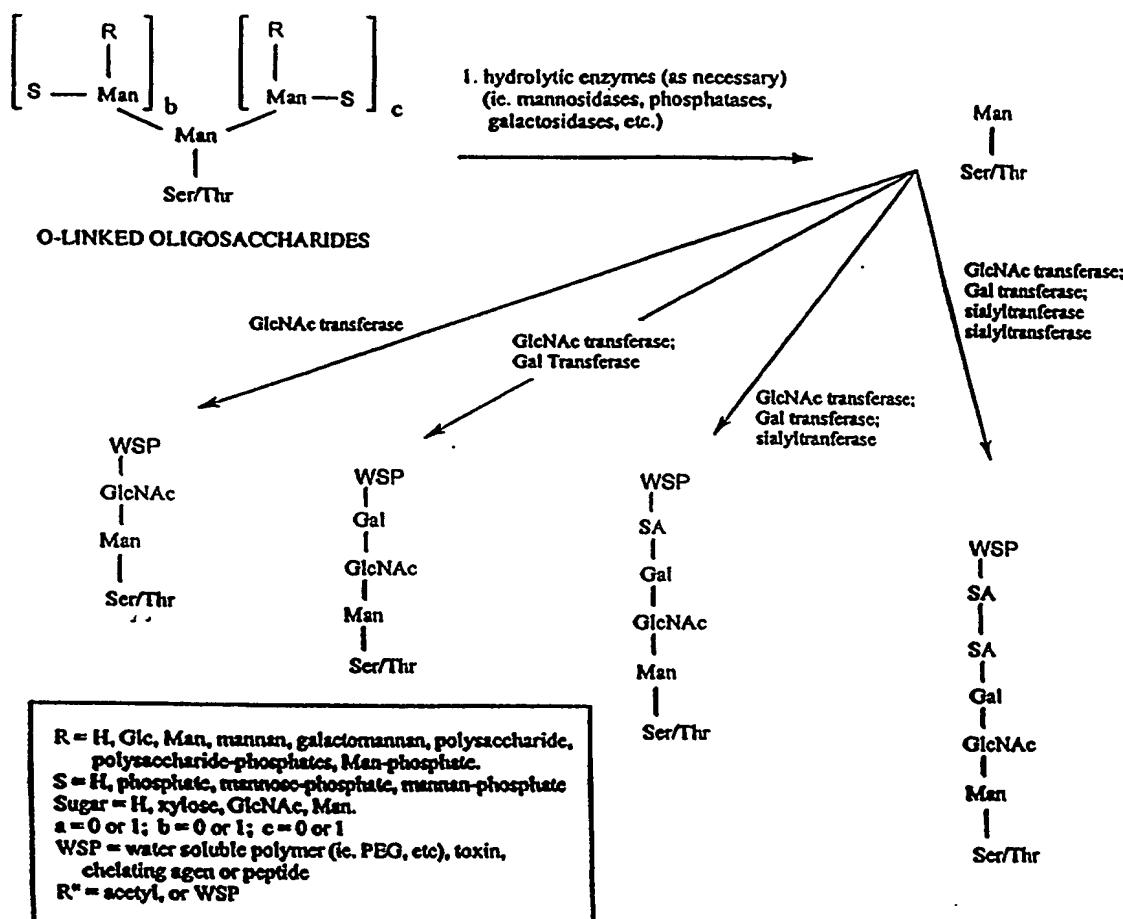


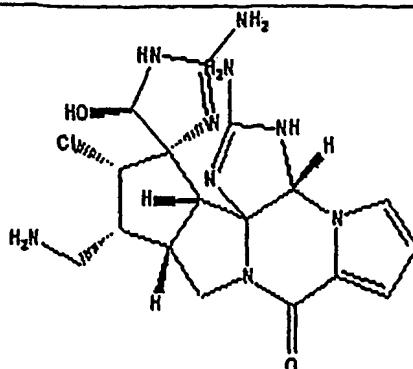
FIG. 9



## Chemical Structure

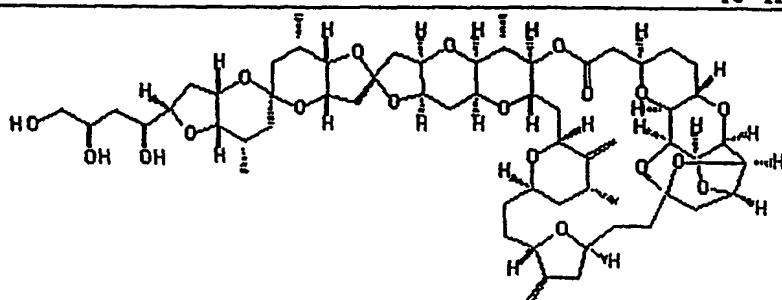
Toxin Name/ Source/ Alternate ID	CAS RN / Analogs	Indication/ Toxicity	Mechanism	Activity (IC50 nM); Tumor Type
SW-163E/ <i>Streptomyces</i> sp SNA 15896/ SW-163E	260794-24-9; 260794-25-0/ SW-163C; SW-163A; SW-163B	Cancer and Antibacterial/ low toxicity (mice ip)	not reported	0.3 P388 0.2 A2780 0.4 KB 1.6 colon 1.3 HL-60
Thiocoraline/ <i>Micromonospora marina</i> (actinomycete)	173046-02-1	Breast Cancer; Melanoma; Non-small lung cancer / not reported	DNA Polymerase alpha inhibitor (blocks cell progression from G1 to S)	lung, colon, CNS melanoma
Trunkamide A <sup>1</sup> / <i>Lissoclinum</i> sp (ascidian)	181758-83-8	Cancer/ not reported	not reported	cell culture (IC50 in micrograms/mL); 0.5 P388; 0.5 A549;

FIG. 11A

0.5 HT-29;  
1.0 MEL-28

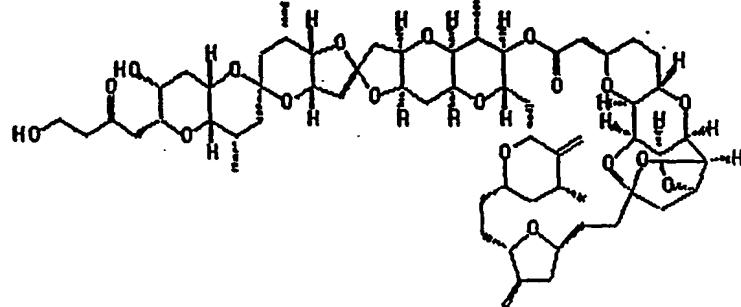
**Palauamine<sup>2/</sup>**  
*Stylorella agminata*  
 (sponge)

148717-58-2   Lung cancer/  
 LD50 (i.p. in mice) is 13  
 mg/Kg   not reported   cell culture (IC50 in  
 micrograms/mL);  
 0.1 P388  
 0.2 A549 (lung)  
 2 HT-29 (colon)  
 10 KB



**Halichondrin B/**  
*Halichondria Okadae,*  
*Axinell Carteri and*  
*Phankell carteri*  
 (sponges)/  
 NSC-609385

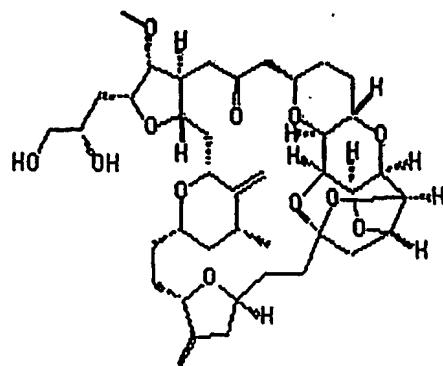
103614-76-2/   cancer/  
 isohomohalichondrin B   myelotoxicity dose  
 limiting (dogs, rats)   antitubulin;   NCI tumor panel;  
 cell cycle inhibitor   GI(50) from 50 nM to  
 (inhibits   0.1 nM;  
 GTP binding   LCS0's from 40  $\mu$ M to  
 to tubulin)   0.1 nM (many 0.1 to 25  
 nM)



**Isohomo-halichondrin B/**  
*Halichondria Okadae,*  
*Axinell Carteri and*  
*Phankell carteri*  
 (sponges)/  
 NSC-650467

157078-48-3/   melanoma, lung, CNS,  
 halichondrin B   colon, ovary/  
 not reported   antitubulin;   IC50's in 0.1 nM range  
 (NCI tumor panel)

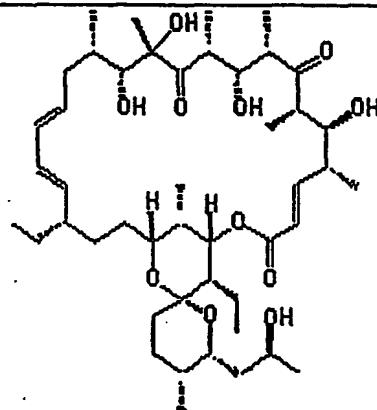
FIG. 11B



**Halichondrin B analogs/ 253128-15-3/ solid tumors/**  
**semi-synthetic starting ER-076349; not reported**  
**from *Halichondria* ER-086526;**  
***Okadai, Axinell Carteri* B-1793;**  
**and *Phankell carteri* B-7389**

tubulin binding agent; disruption of mitotic spindles

cell culture (not reported); animal models active (tumor regression observed) in lymphoma, colon (multi-drug resistant).



**NK-130119/ 132707-68-7 antifungal and**  
***Streptomyces* bottropensis/**  
**NK-130119** not reported 25 ng/mL colon  
 8.5 ng/mL lung

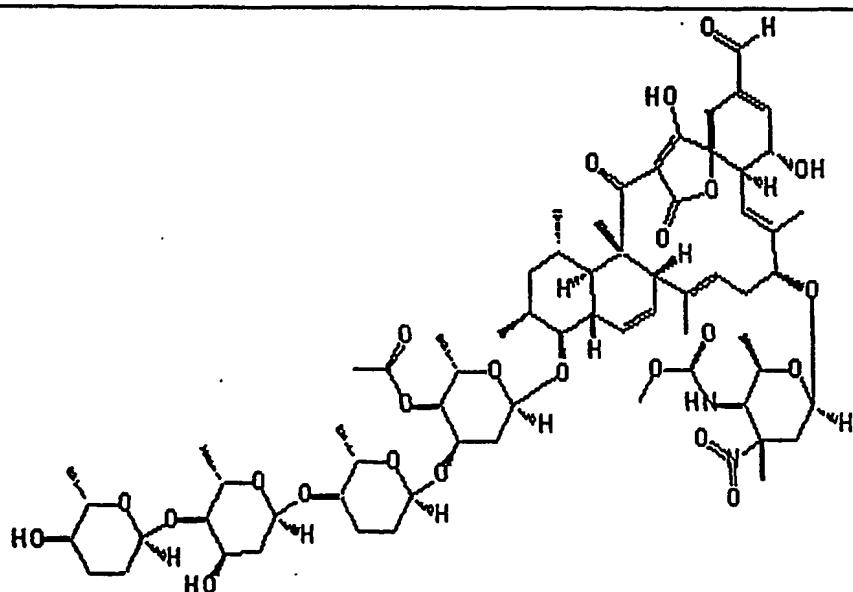


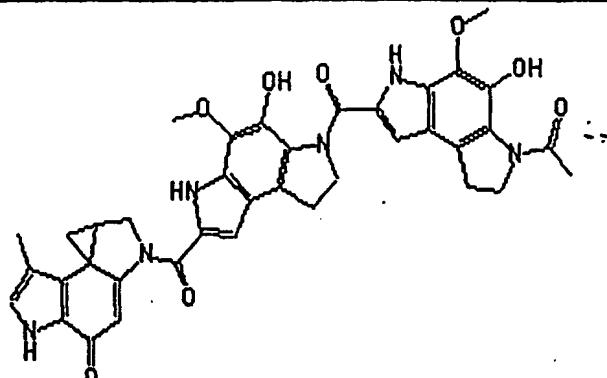
FIG. 11C

**Tetrocarkin A/**  
not reported/  
KF-67544

73666-84-9/  
analogs are  
reported

cancer/  
not reported

inhibits the  
anti-  
apoptotic  
function of  
Bcl2

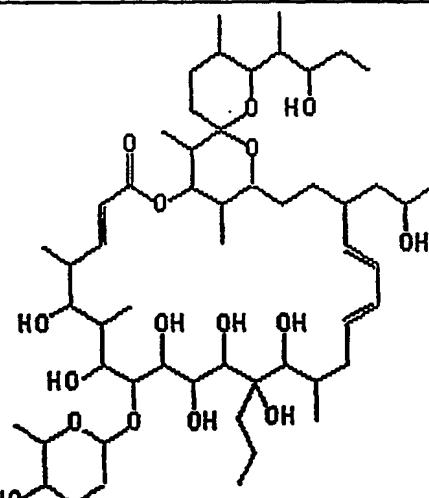


**Gilvusmycin/**  
*Streptomyces* QM16

195052-09-6

cancer/  
not reported

not reported    IC50's in ng/mL:  
0.08 P388  
0.86 K562 (CML)  
0.72 A431 (EC)  
0.75 MKN28 (GI);  
(for all < 1 nM)



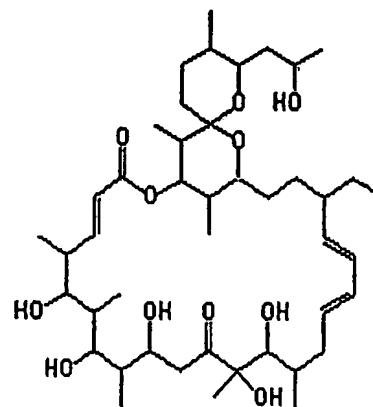
**IB-96212/**  
marine actinomycete/  
IB-96212

220858-11-7/  
IB-96212;  
IB-98214;  
IB-97227

Cancer and  
Antibacterial/  
not reported

not reported    IC50's in ng/mL:  
0.1 P388

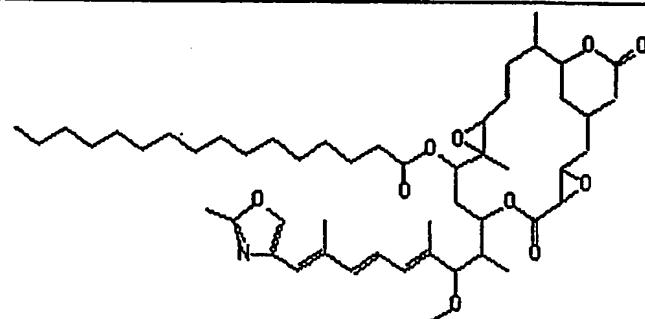
FIG. 11D



BE-56384<sup>3</sup>/  
*Streptomyces* Sp./  
BE-56384

207570-04-5    cancer/  
not reported

not reported    IC50's in ng/mL:  
0.1 P388  
0.29 colon 26  
34 DLD-1  
0.12 PC-13  
0.12 MKM-45



Palmitoylrhizoxin/  
semi-synthetic; *Rhizopus*  
*chinensis*

135819-69-1/  
Analog of  
rhizoxin

cancer/  
binds LDL; less  
cytotoxic than rhizoxin

tubulin  
binding  
agent (cell  
cycle  
inhibitor)

not reported

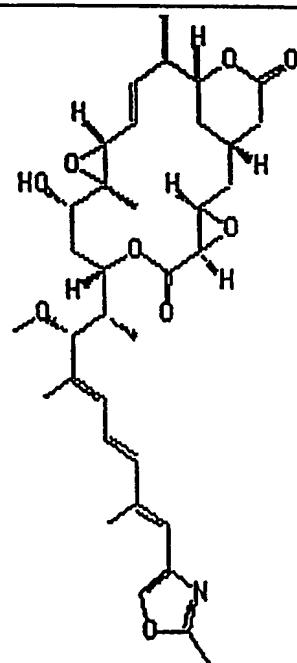
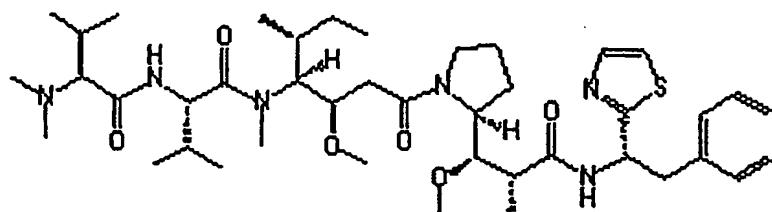
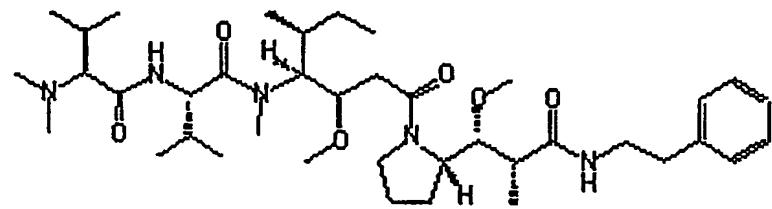


FIG. 11E

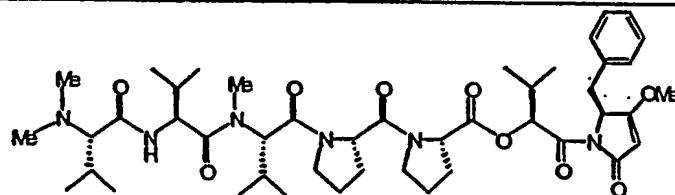
<b>Rhizoxin/</b> <i>Rhizopus chinensis/</i> WF-1360; NSC-332598; FR-900216	95917-95-6; 90996-54-6	melanoma, lung, CNS, colon, ovary, renal, breast, head and neck/ Rapid Drug clearance; High AUC correlates with high toxicity	tubulin binding agent (cell cycle inhibitor)	NCI tumor panel (NSC 332598); log GI50's: 50 nM to 50 fM; log LC50's: 50 $\mu$ M to 0.5 nM (several cell lines at 50 fM).
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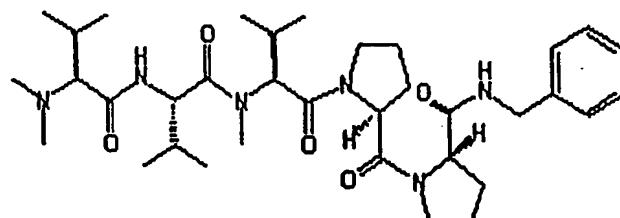
<b>Dolastatin-10/</b> <i>Dolabella auricularia</i> (sea hare)/ NSC-376128	110417-88-4/ other Dolastatins (ie. 15) and analogs	prostate, melanoma, leukemia/ myelotoxicity (at greater than 0.3 pM)	tubulin binding (tubulin aggregation)	NCI tumor panel (60 cell line; GI50); 25 nM to 1 pM (most < 1 nM) (three cell lines $\mu$ M)
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<b>soblidotin/</b> synthetic/ TZT-1027; auristatin PE	149606-27-9/ analogs prepared	cancer (pancreas, esophageal colon, breast, lung, etc) / MTD was 1.8 mg/Kg (IV); toxicity not reported	tubulin binding agent	cell culture: colon, melanoma, MS076 tumors, P388 with 75- 85% inhibition (dose not reported)
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<b>Dolastatin-15/</b> <i>Dolabella auricularia</i> (sea hare)	not reported/ other Dolastatins (ie. 15) and analogs	cancer/ not reported	Tubulin binding (tubuline aggregation)	NCI tumor panel (60 cell line; GI50); 25 nM to 39 pM (most < 1 nM) (one cell line 2.5 $\mu$ M); most active in breast
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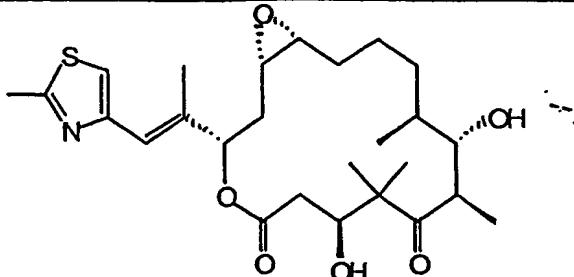
<b>Cemadotin<sup>4</sup>/</b>	1159776-69-	melanoma/	tubulin	NCI tumor panel (NCS)
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FIG. 11F

**Synthetic; Parent 9/**  
**Dolastatin-15 was isolated many analogs**  
**from *Dolabella auricularia* (sea hare)/**  
**LU-103793; NSC D-669356**

**hypertension, myocardial binding**  
**ischemia and**  
**myelosuppression were**  
**dose-limiting toxicities.**

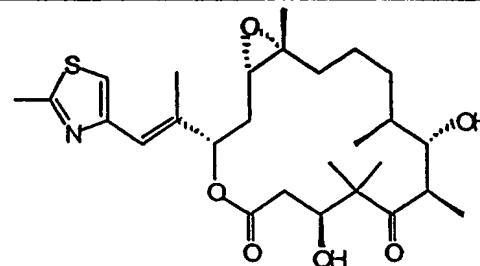
**D-669356); active in**  
**breast, ovary,**  
**endometrial, sarcomas**  
**and drug resistant cell**  
**lines. Data not public.**



**Epothilone A/**  
**not reported/**  
**Synthetic or isolated from**  
**many analogs**  
**cancer/**  
***Sorangium cellulosum***  
**(myxococcales) strain**  
**So ce90)**

**tubulin**  
**binding**  
**(tubulin**  
**polymeriza-**  
**tion)**

**IC50's of;**  
**1.5 nM MCF-7 (breast)**  
**27.1 nM MCF-7/ADR**  
**2.1 nM KB-31**  
**(melanoma)**  
**3.2 nM HCT-116**

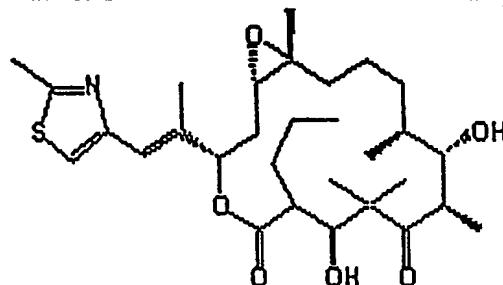


**Epothilone B/**  
**152044054-7/**  
**Synthetic or isolated from**  
**many analogs**  
***Sorangium cellulosum***  
**(myxococcales) strain So**  
**ce90) /**  
**EPO-906**

**Solid tumors (breast,**  
**ovarian, etc)/**  
**well tolerated; t1/2 of**  
**2.5 hrs; partial**  
**responses (phase I);**  
**diarrhea major side**  
**effect.**

**tubulin**  
**binding**  
**(tubulin**  
**polymeriza-**  
**tion)**

**IC50's of;**  
**0.18 nM MCF-7**  
**(breast)**  
**2.92 nM MCF-7/ADR**  
**0.19 nM KB-31**  
**(melanoma)**  
**0.42 nM HCT-116;**  
**broad activity reported**



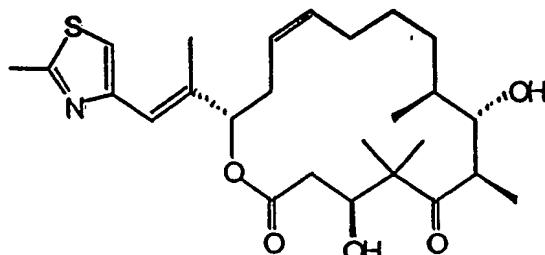
**Epothilone Analog /**  
**Synthetic or semi-**  
**synthetic; Original lead,**  
**Epothilone A, isolated**  
**from *Sorangium***  
***cellulosum***  
**(myxococcales) strain So**  
**ce90)/**  
**ZK-EPO**

**not reported /**  
**hundreds of**  
**analogs**  
**cancer/**  
**not reported**

**tubulin**  
**binding**  
**(tubulin**  
**polymeriza-**  
**tion)**

**IC50's of 0.30 to**  
**1.80 nM in various**  
**tumor cell lines;**  
**active in drug resistant**  
**cell lines**

FIG. 11G



**Epothilone D /**  
**Epothilone D, isolated**  
**from *Sorangium***  
***cellulosum***  
 (myxococcales) strain So  
 ce90)/  
**KOS-862**

189452-10-9/ Solid tumors (breast, ovarian, etc)/ emesis and anemia; t1/2 of 5-10 hrs.

tubulin binding (tubulin polymerization)

NCI tumor panel (NSC-703147; IC50); 0.19 nM KB-31 (melanoma) 0.42 nM HCT-116; broad activity reported

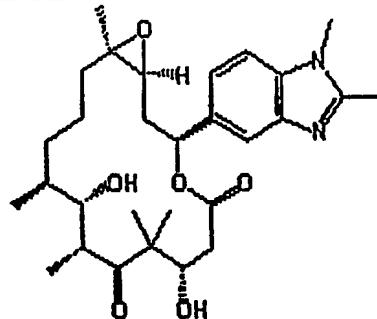
#### Structure Not Identified

**Epothilone D analog<sup>5/</sup>**  
 Synthetic or semi-synthetic; Original lead, Epothilone D, isolated from *Sorangium cellulosum* (myxococcales) strain So ce90)/  
**KOS-166-24**

189453-10-9/ Solid tumors; hundreds of not reported analogs

tubulin binding (tubulin polymerization)

not reported



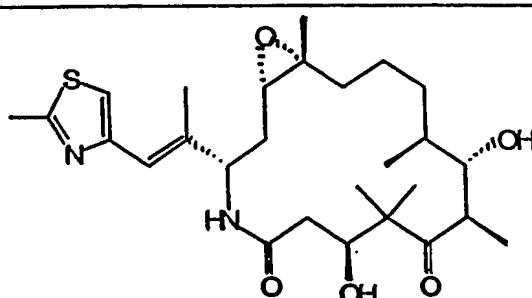
**Epothilone Analog /**  
 Synthetic; Original lead, Epothilone A, isolated from *Sorangium cellulosum* (myxococcales) strain So ce90)/  
**CGP-85715**

not reported/ hundreds of analogs

cancer; not reported

tubulin binding (tubulin polymerization)

not reported



**Epothilone Analog/**

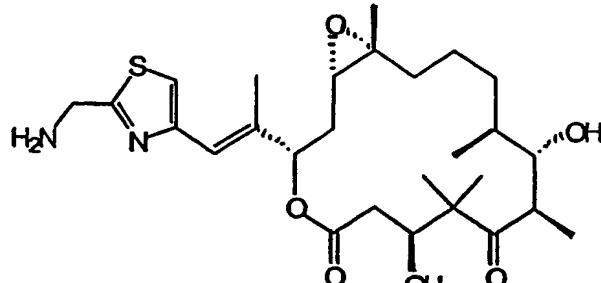
219989-84-1/ non-small cell Lung,

tubulin

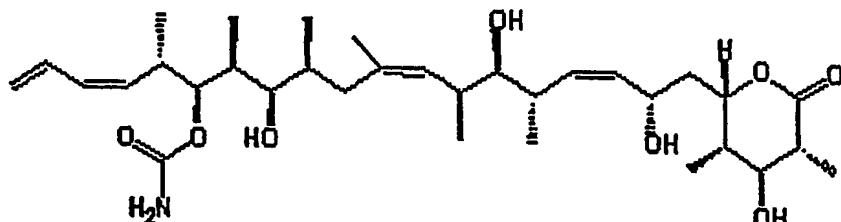
NCI tumor Panel (NSC-

**FIG. 11H**

Synthetic or semi-synthetic; Original lead, Epothilone B, isolated from <i>Sorangium cellulosum</i> (myxococcales) strain So ce90)/ <u>BMS-247550</u>	hundreds of analogs	breast, stomach tumor (objective responses in breast ovarian and lung)/ sever toxicity (fatigue, anorexia, nausea, vomiting, neuropathy myalgia)	binding (tubulin polymerizati on)	710428 & NSC- 710468); 8-32 nM (NCI data not available)
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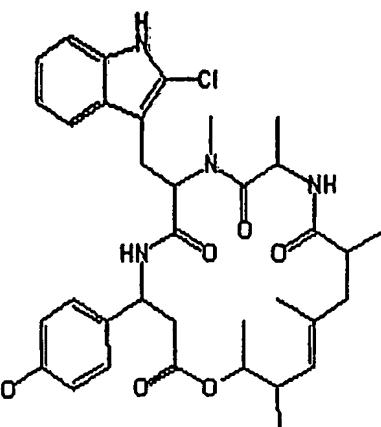


Epothilone Analog / Synthetic or semi-synthetic; Original lead, Epothilone B, isolated from <i>Sorangium cellulosum</i> (myxococcales) strain So ce90)/ <u>BMS-310705</u>	not reported/ hundreds of analogs	advanced cancers/ adverse events (diarrhea, nausea, vomiting, fatigue, neutropenia); t1/2 of 3.5 hrs; improved water solubility to BMS 247550.	tubulin binding (tubulin polymerizati on)	broad activity with IC50's of 0.7 to 10 nM
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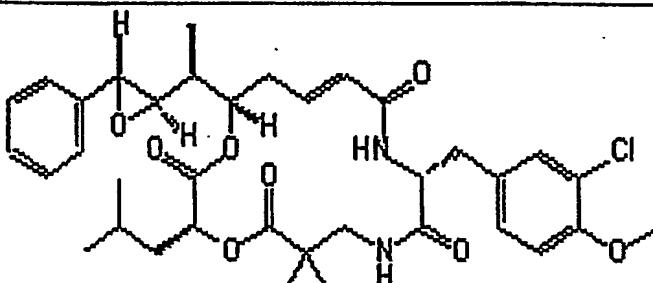


Discodermolide / synthetic; originally isolated from <i>Discodermia dissoluta</i> (deep water sponge); rare compound (7 mg per 0.5 Kg sponge/ XAA-296	127943-53-7/ analogs less potent	solid tumors/ not reported; 100-fold increase in water solubility over taxol	tubulin stabilizing agent (similar to taxol)	Broad activity (A549- nsclung, prostate, P388, ovarian with IC50's about 10 nM) including multi-drug resistant cell lines;
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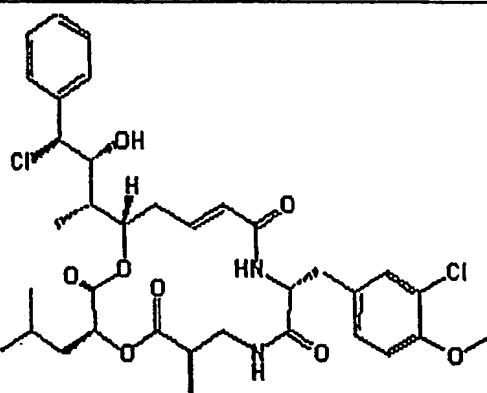
FIG. 11I



Chondramide D/ not reported	172430-63-6	cancer/ not reported	tubulin binding agent; actin polymeriza- tion inhibitor	5 nM A-549 (epidermoid carcinoma) 15 nM A-498 (kidney) 14 nM A549 (lung) 5 nM SK-OV-3 (ovary) 3 nM U-937 (lymphoma)
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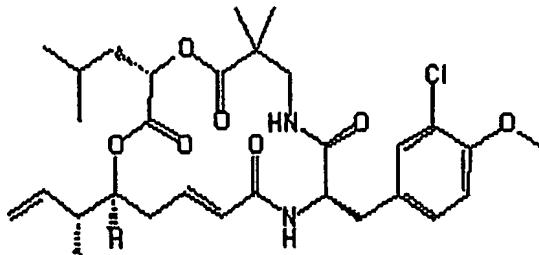
Cryptophycin analogs (including 52, 55 and others) <sup>6/</sup> <i>Nostoc</i> sp GSV 224 (blue- green algae) isolated Cryptophycin 1./ LY-355703; Ly-355702; NSC-667642	204990-60-3 and 186256- 67-7/ many potent analogs prepared at Lilly	solid tumors, colon cancer/ Phase II studies halted because of severe toxicity with one death resulting from drug;	tubulin polymeriza- tion inhibitor	broad activity (lung, breast, colon, leukemia) with IC50's of 2 to 40 pM; active against multi-drug resistance cell lines (resistant to MDR pump). NCI tumor panel, GI50's from 100 nM to 10 pM; LC50's from 100 nM to 25 pM.
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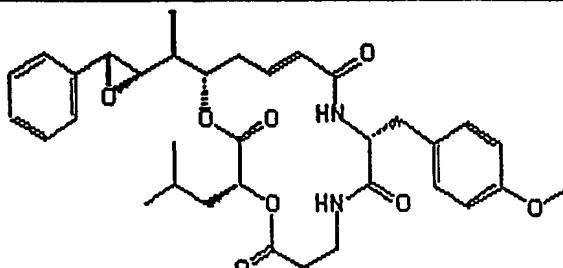
Cryptophycin 8/	168482-36-8;	solid tumors/	tubulin	broad spectrum
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FIG. 11J

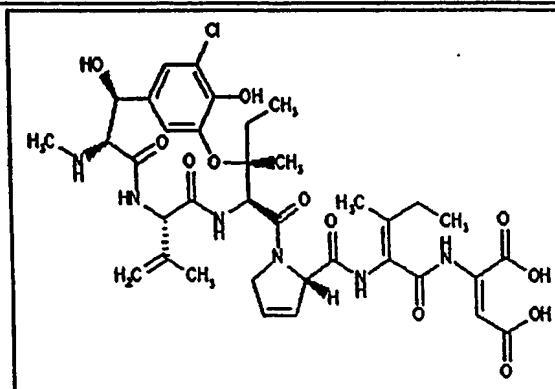
semi-synthetic; starting material from <i>Nostoc</i> sp.	168482-40-4; not reported 18665-94-1; 124689-65-2; 125546-14-7/ cryptophycin 5, 15 and 35	polymerization inhibitor	anticancer activity (cell culture) including multi-drug resistant tumors
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Cryptophycin analogs <sup>7/</sup> synthetic; semi-synthetic, starting material from <i>Nostoc</i> sp./ LY-404291	219660-54-5/ LY-404292	solid tumors/ not reported	topoisomerase inhibitors	not reported
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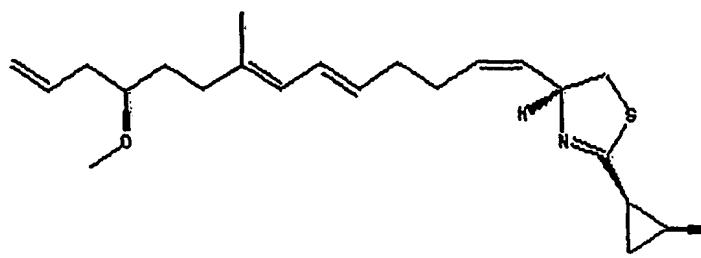


Arenastatin A analogs <sup>8/</sup> <i>Dysidea arenaria</i> (marine sponge)/ Cryptophycin B; NSC-670038	not reported/ analog prepared	cancer/ not reported	inhibits tubulin polymerization	8.7 nM (5 pg/mL) KB (nasopharyngeal); NCI tumor panel (GI50's); 100 pM to 3 pM
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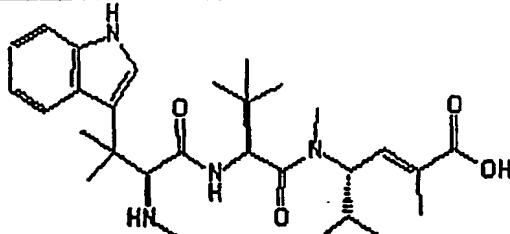
Phomopsin A/ <i>Diaporte toxicus</i> or <i>Phomopsin leptostromiformis</i> (fungi)	not reported	Liver cancer (not as potent in other cancers)/ not reported	tubulin binding agent	potent anticancer activity especially against liver cancer
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FIG. 11K



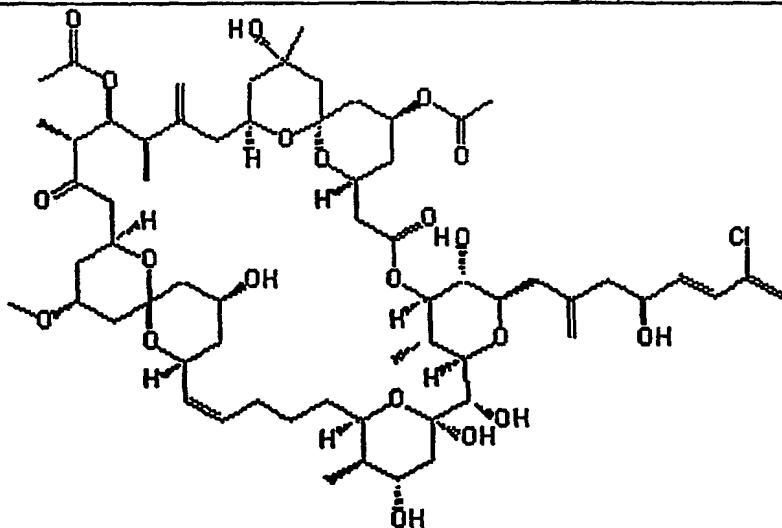
**Curacin A and analogs/** 155233-30-0/ **Cancer/**  
***Lyngbya majuscula* (blue** **analogs have** **not reported**  
**green cyanobacterium)** **been prepared**

**Tubulin** **broad activity (cancer**  
**cell lines); 1-29 nM**



**Hemiasterlins A & B** **not reported/** **Cancer/**  
**and analogs<sup>9/</sup>** **criamide A &** **not reported**  
***Cymbastela* sp.** **B;** **geodiamolid-**  
**G**

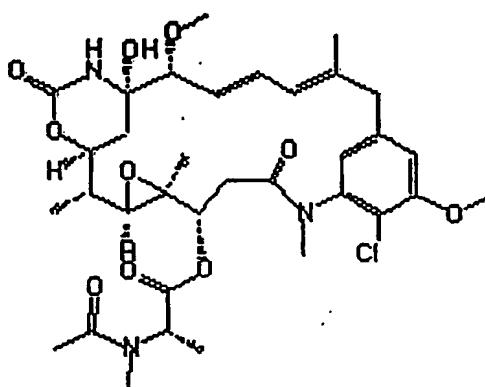
**Antimitotic** **broad activity:**  
**agent** **0.3-3 nM MCF7**  
**(tubulin** **(breast);**  
**binding** **0.4 ng/mL P388**  
**agent)**



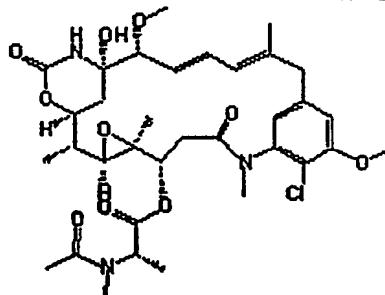
**Spongistatins (1-9)<sup>10/</sup>** 149715-96-8; **cancer/**  
***Spirastrell spinispirulifera*** 158734-18-0; **not reported**  
**(sea sponge)** 158681-42-6;  
158080-65-0;  
150642-07-2;  
153698-80-7;  
153745-94-9;  
150624-44-5;  
158734-19-1/  
other  
spongistatins

**tubulin** **binding**  
**agent** **Most potent compounds**  
**ever tested in NCI panel**  
**cell line (mean GI50's**  
**of 0.1 nM;**  
**Spongistatin-1 GI50's**  
**of 0.025-0.035 nM with**  
**extremely potent**  
**activity against a subset**  
**of highly**  
**chemoresistant tumor**  
**types**

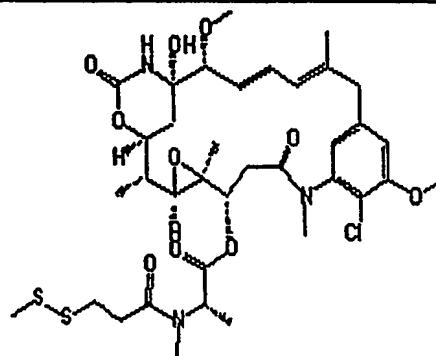
FIG. 11L



Maytansine/ <i>Maytenus</i> sp./ NSC-153858	35846-53-8/ other related macrolides	cancer/ severe toxicity	tubulin binding agent (causes extensive disassembly of the microtubule and totally prevents tubulin spiralizaiton)	Broad Activity in NCI tumor panel (NSC- 153858; NSC-153858); NCI tumor panel, GI50's from 3 $\mu$ M to 0.1 pM; LC50's from 250 $\mu$ M to 10 pM. Two different experiments gave very different potencies.
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Maytansine-IgG(EGFR directed)-conjugate <sup>11</sup> / semi-synthetic; starting material from <i>Maytenus</i> sp.	not reported/ other related macrolides	breast , head and neck, Squamous cell carcinoma/ not reported	EGFR binding and tubulin binding	not reported
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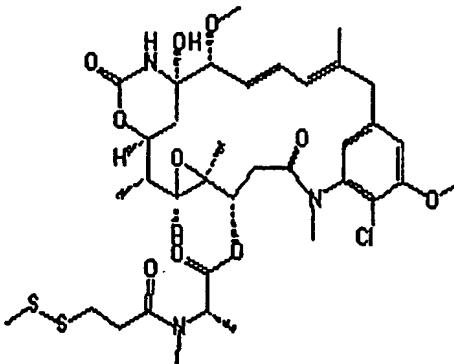
Maytansine-IgG(EGFR directed)-conjugate <sup>12</sup> , 3.5 drug molecules per IgG/ semi-synthetic; starting material from <i>Maytenus</i>	not reported/ other related macrolides	Neuroendocrine, small- cell lung, carcinoma/ mild toxicity (fatigue, nausea, headaches and mild peripheral	CD56 binding and tubulin binding	antigen-specific cytotoxicity (cell culture; epidermal, breast, renal ovarian colon) with IC50's of
--	--	--	---	---

FIG. 11M

sp./  
huN901-DM1

neuropathy); no hematological toxicity; MTD 60 mg/Kg, I.V., weekly for 4 weeks; only stable disease reported (humans)

10-40 pM; animal studies (miceSCLC tumor-alone and in combination with taxol or cisplatin completely eliminated tumors).



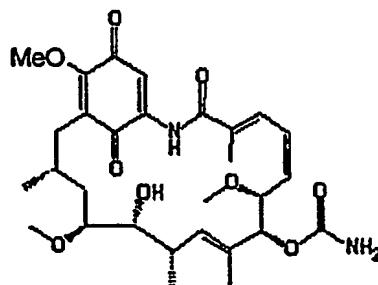
Maytansine-IgG(CEA antigen)-conjugate<sup>13</sup>, 4 drug molecules per IgG/ semi-synthetic; starting material from *Maytenus* sp./  
C424-DM1

not reported/ other related macrolides

non-small-cell lung, carcinoma pancreas, lung, colon/ mild toxicity (fatigue, nausea, headaches and mild peripheral neuropathy); pancreatic lipase elevated; MTD 88 mg/Kg, I.V., every 21 days; only stable disease reported (humans); t<sub>1/2</sub> was 44 hr.

CEA binding and tubulin binding

antigen-specific cytotoxicity (cell culture; epidermal, breast, renal ovarian colon) with IC50's of 10-40 pM; animal studies (mice: melanoma [COLO-205]—alone and in combination with taxol or cisplatin completely eliminated tumors);



Geldanamycin /  
*Streptomyces*  
*hygroscopicus* var.  
Geldanus/  
NSC-212518; Antibiotic  
U 29135; NSC-122750

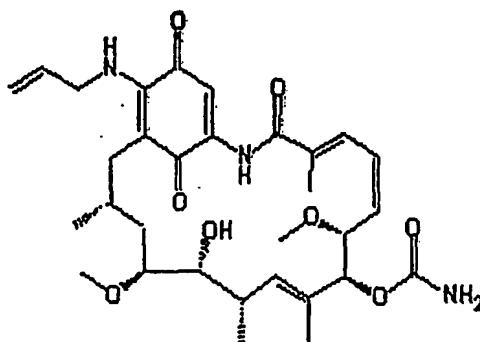
30562-34-6/  
natural derivatives

cancer/ not reported

binds Hsp 90 chaperone and inhibits function

NCI tumor panel (cell culture); 5.3 to 100 nM; most active in colon, lung and leukemia. NCI tumor panel, GI50's from 10  $\mu$ M to 0.1 nM; LC50's from 100  $\mu$ M to 100 nM. Two assays with very different potencies.

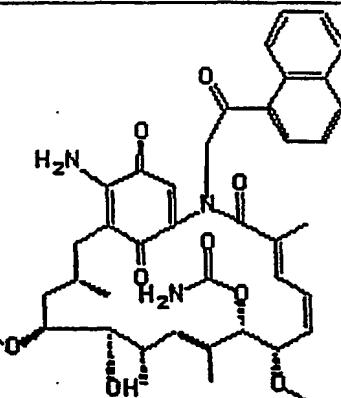
FIG. 11N



**Geldanamycin Analog/**  
semi-synthetic; /  
CP-127374; 17-AAG;  
NSC-330507

745747-14-7/ solid tumors/  
Kosan, NCI Dose limiting toxicities  
and UK (anemia, anorexia,  
looking for diarrhea, nausea and  
analogs with vomiting); t<sub>1/2</sub> (i.v.) is  
longer t<sub>1/2</sub> about 90 min; no  
and oral objective responses  
activity; measured at 88 mg/Kg  
analogs (i.v. daily for 5 days,  
include: NSC- every 21 days);  
255110;  
682300;  
683661;  
683663.

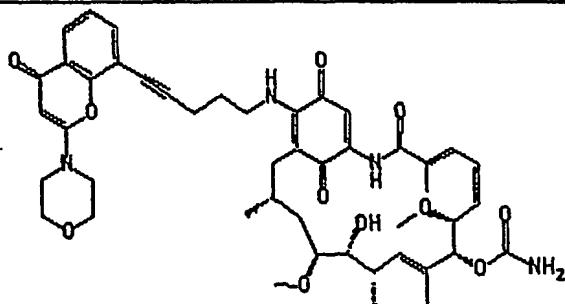
binds Hsp 90 cell culture (not  
chaperone reported); animal  
and inhibits models active (tumor  
function regression observed) in  
breast, ovary,  
melanoma, colon.



**Geldanamycin analog/**  
semi-synthetic; /  
CP-202567

not reported/ solid tumors/  
analogs not reported  
prepared

binds Hsp 90 not reported  
chaperone  
and inhibits  
function



**Geldanamycin**  
**conjugates/**  
**semi-synthetic; /**  
**LY-294002-GM; PI3K-1-**  
**GM**

345232-44-2/ breast/  
analogs not reported  
prepared

binds Hsp 90 cell culture (no  
chaperone reported); animal  
and inhibits models performed  
function;  
binds and

FIG. 11O

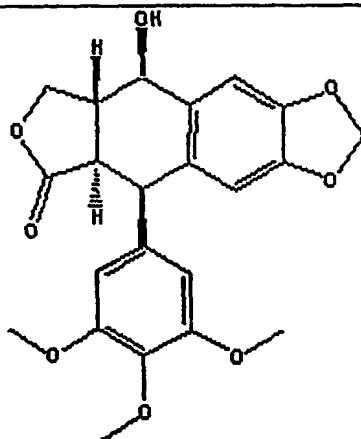
inhibits PI-3  
kinase

Structure Not Reported

<b>Geldanamycin Analog/ not reported/ CNF-101</b>	not reported/ analog prepared	breast, prostate/ not reported	binds Hsp 90 not reported chaperone and inhibits function
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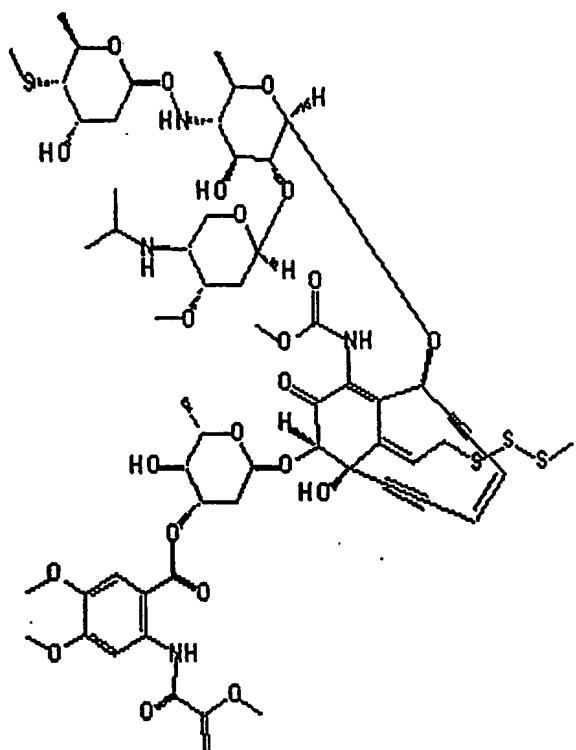
Structure Not Reported

<b>Geldanamycin- testosterone conjugate/ semi-synthetic/ GMT-1</b>	not reported/ analog prepared	prostate/ not reported	binds Hsp 90 not reported; conjugate chaperone has a 15-fold selective and inhibits cytotoxicity for function and androgen positive testosterone prostate cells receptors where it is internalized
--	-------------------------------------	---------------------------	---



<b>Podophyllotoxin/ <i>Podophyllum</i> sp.</b>	<b>518-28-5/ many analogs</b>	<b>Verruca vulgaris, Condyloma/ severe toxicity when given i.v. or s.c.</b>	<b>tubulin inhibitor and topoisomerase inhibitor</b>	<b>broad activity (cell culture) with IC50's in μM range</b>
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FIG. 11P



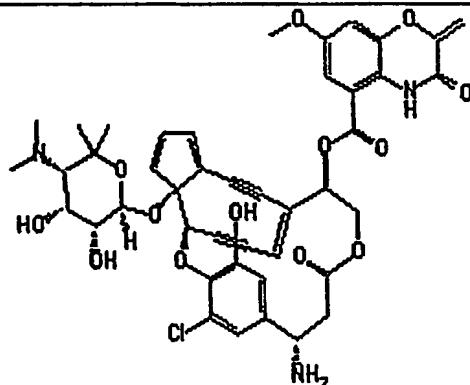
esperamicin-A1/  
not known/  
BBM-1675A1; BMY-  
28175; GGM-1675

99674-26-7

cancer/  
not reported (suspected  
severe toxicity)

DNA  
cleaving  
agent

highly potent activity  
(cell culture); animal  
models highly potent  
with optimal dose of  
0.16 micrograms/Kg



C-1027<sup>14</sup>/  
*Streptomyces setonii* C-  
1027/  
C-1027

120177-69-7

cancer (examined  
hepatoma, breast, lung  
and leukemia/  
not reported)

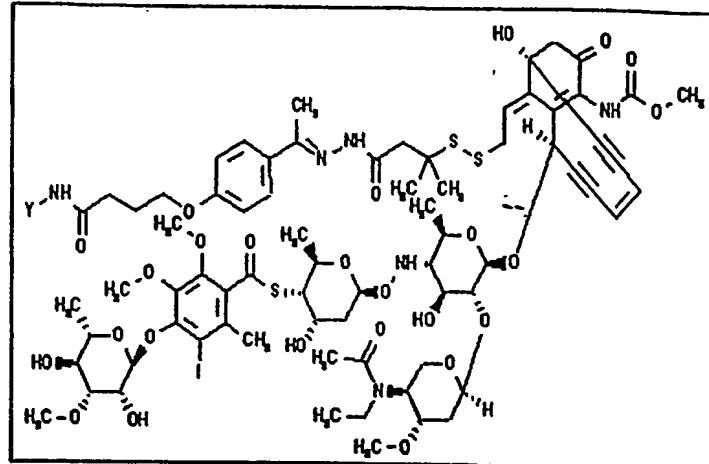
DNA  
cleaving  
agent

extremely potent (cell  
culture) IC50's in pM  
and fM; conjugated to  
antibodies the potency  
remains the same (ie.  
5.5 to 42 pM);

FIG. 11Q



$m = 0.5 - 1.5$   
 Pr = proteinaceous carrier  
 W = calicheamicin minus Me-S-S-S  
 X = linker  
 Y = antibody P76.6



Calicheamicin-  
IgG(CD33 antigen)-  
conjugate<sup>15</sup>/  
semi-synthetic:  
*Micromonospora*  
*echinosporal*  
gemtuzumab ozogamicin;  
mylotarg; WAY-CMA-  
676; CMA-676; CDP-  
771

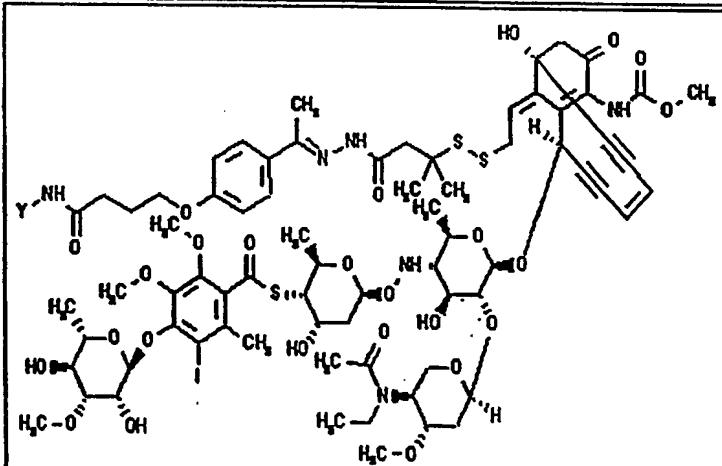
113440-58-7; AML/  
220578-59-6/ mild toxicity  
several  
reported in  
patents

## DNA cleaving agent

Kills CD33+ cells (HL-60, NOMO-1, and NKM-1) at 100 ng/mL; MDR cell lines are not effected by the drug.

$\Pr(X \leq 5)$

**m = 0.5 - 15**  
**Pr = prothrombinic carrier**  
**W = calicheamicin minus Me-S-S-S**  
**X = linker**  
**Y = antibody P76.6**



**Calicheamicin-IgG-conjugates<sup>16</sup>/semi-synthetic:  
*Micromonospora echinospora***

113440-58-7; cancer/  
220578-59-6 not reported

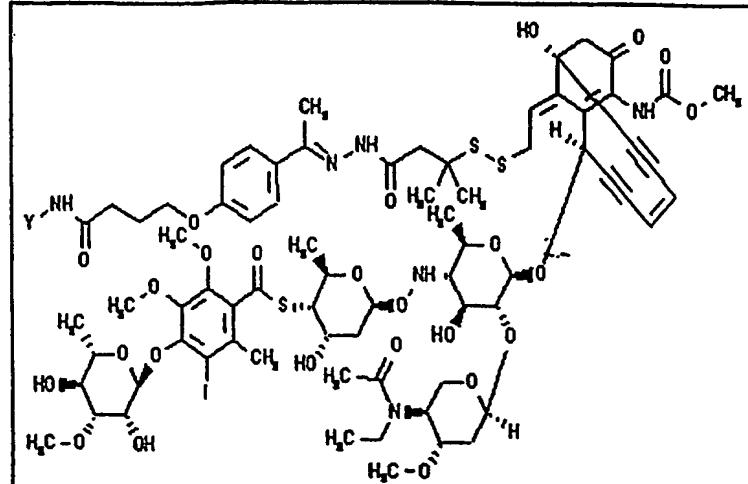
## DNA cleaving agent

TBD

FIG. 11R

$\text{Pr}(\text{X}-\text{S}-\text{W})_m$ 

$m = 0.5 - 15$   
 $\text{Pr} = \text{proteinaceous carrier}$   
 $\text{W} = \text{calicheamicin minus Me-S-SS}$   
 $\text{X} = \text{linker}$   
 $\text{Y} = \text{antibody P76.6}$



**Calicheamicin-IgG(OBA1 antigen) conjugate/ semi-synthetic:**  
*Micromonospora echinopspora/ OBA1-H8*

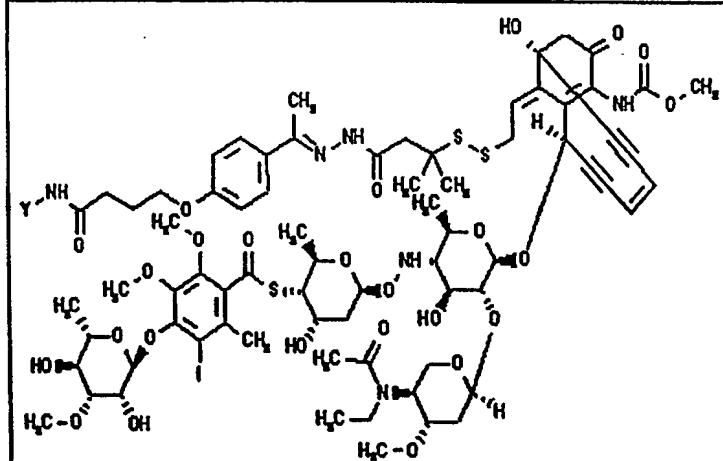
not reported    cancer/ not reported

DNA cleaving agent

all human cancer; data not reported

 $\text{Pr}(\text{X}-\text{S}-\text{W})_m$ 

$m = 0.5 - 15$   
 $\text{Pr} = \text{proteinaceous carrier}$   
 $\text{W} = \text{calicheamicin minus Me-S-SS}$   
 $\text{X} = \text{linker}$   
 $\text{Y} = \text{antibody P76.6}$



**Calicheamicin-IgG(CD22 antigen) conjugate/ semi-synthetic:**  
*Micromonospora echinopspora/ CMC-544*

not reported

non-Hodgkin lymphoma, DNA cancer/ not reported

cleaving agent

all human cancer; data not reported

**partially esterified polystyrene maleic acid copolymer (SMA) conjugated to neocarzinostatin (NCS)**

**Neocarzinostatin<sup>17</sup>**  
semi-synthetic;  
*Streptomyces carconistaticus/*  
*Zinostatin stimalamer; YM-881; YM-16881*

123760-07-6; 9014-02-2    liver cancer and brain cancer/ not reported

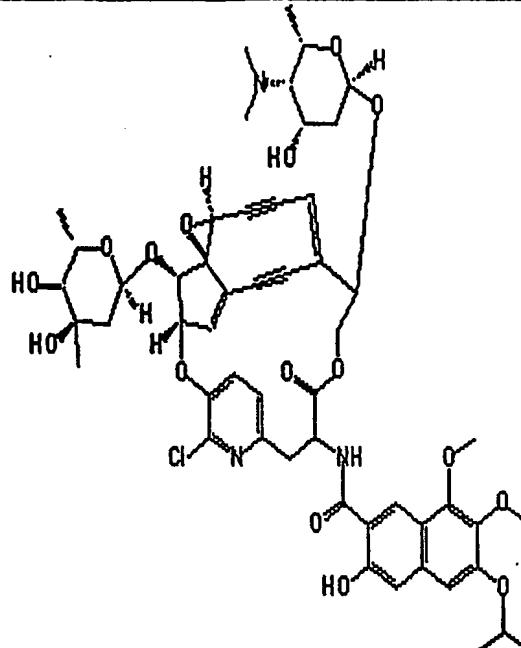
DNA cleaving agent

cell culture data not reported.

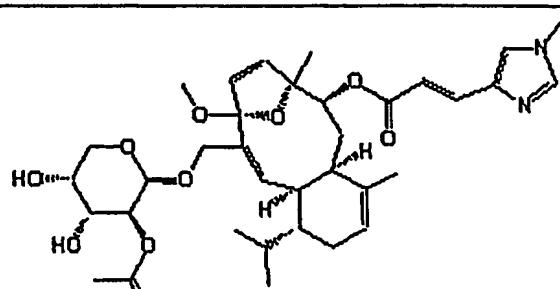
**FIG. 11S**

## IgG (TES-23)-conjugated to neocarzinostatin

Neocarzinostatin/ not reported/ TES-23-NCS	not reported	solid tumors/ toxicity not reported; the cleaving TES-23 antibody (without anticancer agent) was as effective at eliminating tumors as the drug conjugated protein	DNA agent and immunostim- ulator	cell culture data not reported.
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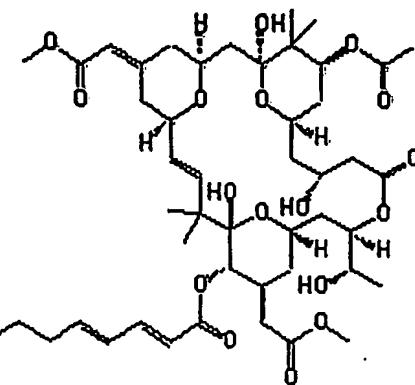


Kedarcidin <sup>18</sup> / <i>Streptoalloteichus</i> sp NOV strain L5856, ATCC 53650/ NSC-646276	128512-40-3; 128512-39-0/ chromophore and protein conjugate	cancer/ not reported	DNA cleaving agent	cell culture (IC50's in ng/mL), 0.4 HCT116; 0.3 HCT116/VP35; 0.3 HCT116/VM46; 0.2 A2780; 1.3 A2780/DDP. animal models in P388 and B-16 melanoma. NCI tumor panel, GI50's from 50 $\mu$ M to 5 $\mu$ M.
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Eleutherobins/ marine coral	174545-76-7/ sarcodictyins (marine coral)	cancer/ not reported	tubulin binding agent	similar potency to taxol; not effective against MDR cell lines
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FIG. 11T

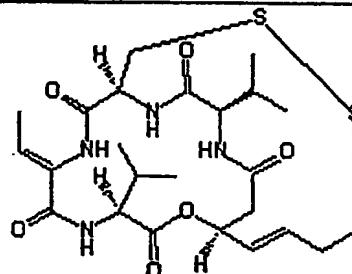


**Bryostatin-1/**  
*Bugula neritina* (marine  
 bryozoan)/  
 GMY-45618; NSC-  
 339555

83314-01-6

leukemia, melanoma,  
 lung, cancer/  
 myalgia; accumulated  
 toxicity; poor water  
 solubility; dose limiting  
 toxicity

immunostim- not reported  
 ulant (TNF,  
 GMCSF,  
 etc);  
 enhances cell  
 kill by  
 current  
 anticancer  
 agents



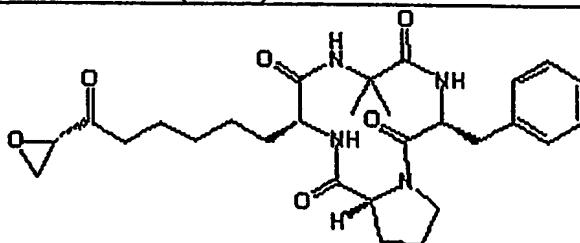
**FR-901228/**  
*Chromobacterium*  
*violaceum* strain 968/  
 NSC-63-176; FK-228

128517-07-7

leukemia, T-cell  
 lymphoma, cancer/  
 toxic doses (LD50) 6.4  
 and 10 mg/Kg, ip and iv  
 respectively; GI  
 toxicity, lymphoid  
 atrophy; dose limiting  
 toxicity (human) 18  
 mg/Kg, t1/2 of 8 hrs  
 (human)

histone  
 deacetylase  
 inhibitor

In vitro cell lines (NCI  
 tumor panel);  
 IC50's of between 0.56  
 and 4.1 nM (breast,  
 lung, gastric colon,  
 leukemia)



**Chlamydocin/**  
 not reported

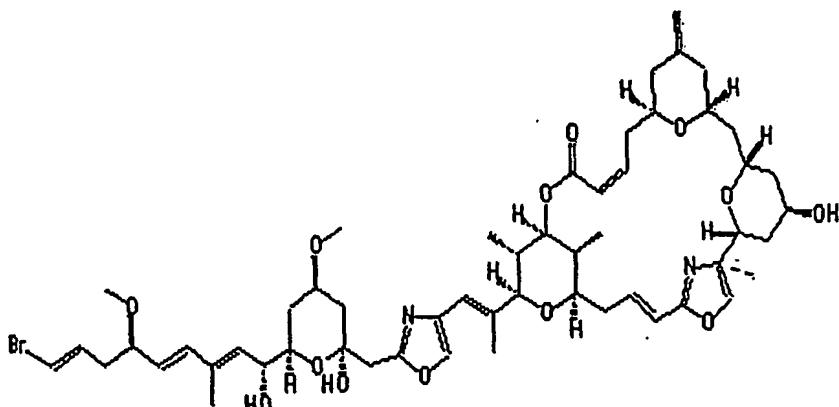
53342-16-8

cancer/  
 not reported

histone  
 deacetylase  
 inhibitor

not reported (cell  
 culture);  
 inhibits histone  
 deacetylase at an IC50  
 of 1.3 nM

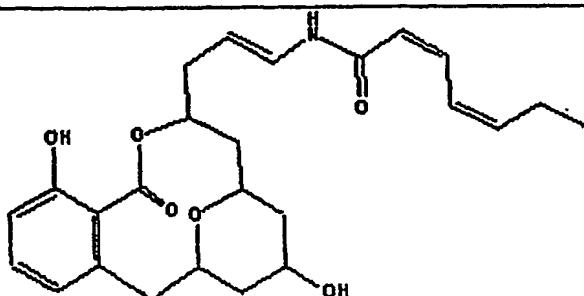
FIG. 11U



**Phorboxazole A<sup>19</sup>/  
marine sponge**

181377-57-1; leukemia, myeloma/  
165689-31-6; not reported  
180911-82-4;  
165883-76-1/  
analogs  
prepared

not reported  
(induces apoptosis)  
NCI tumor panel  
(details not reported);  
IC50's of 1-10 nM. The  
inhibition values  
(clonogenic growth of  
human cancer cells) at  
10 nM ranged from 6.2  
to > 99.9% against  
**NALM-6** human B-  
lineage acute  
lymphoblastic  
leukemia cells, BT-20  
breast cancer cells and  
U373 glioblastoma  
cells, with the specified  
compound showing  
inhibition values in the  
range of 42.4 to >  
99.9% against these cell  
lines.; IC50's are nM  
for MDR cell lines.

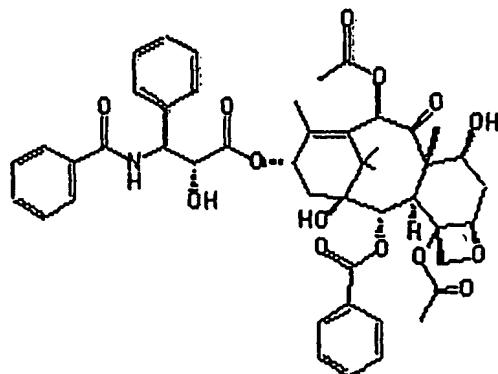


**Apicularen A/  
*Chondromyces robustus***

220757-06-2/  
natural  
derivatives

cancer/  
not reported  
not reported  
IC50's of 0.1 to 3  
ng/mL (KB-3-A, KB-  
Va, K562, HL60, U937,  
A498, A549, PV3 and  
SK-OV3)

**FIG. 11V**



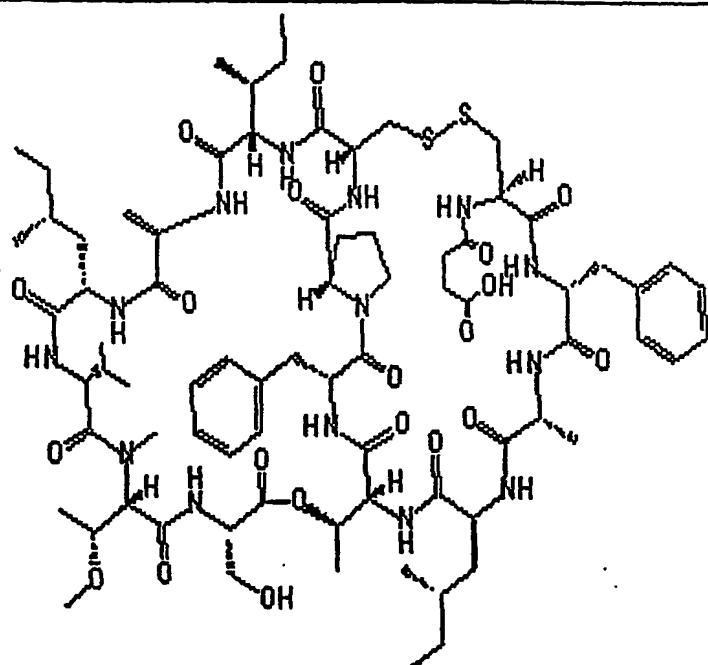
**Taxol/**  
Pacific yew and fungi/  
Paclitaxel; NSC-125973

33069624/  
many analogs

cancer; breast, prostate,  
ovary, colon, lung, head  
& neck, etc./  
severe toxicity (grade III  
and IV)

tubulin  
binding  
agent

NCI tumor panel;  
GI50's of 3 nM to 1  
μM;  
TGI 50 nM to 25 μM



**Vitlevuamide/**  
*Didemnum cuculliferum*  
or *Polysyncraton*  
*lithostrotum*

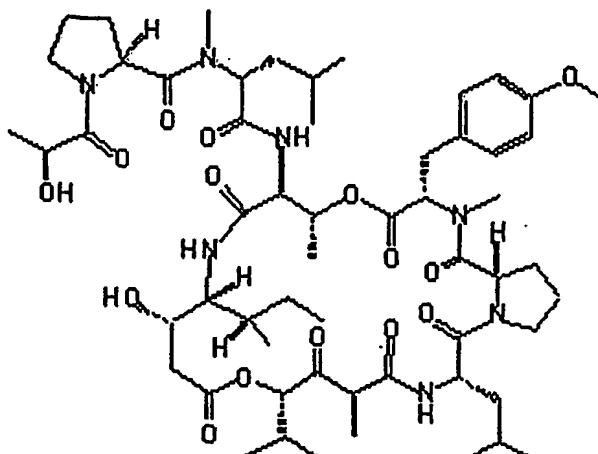
191681-63-7

cancer/  
not reported

tubulin  
binding  
agent

cell culture; IC50's of  
6-311 nM (panel of  
tumor cell lines  
HCT116 cells, A549  
cells, SK-MEL-5 cells  
A498 cells). The  
increase in lifespan  
(ILS) for CDF1 mice  
after ip injection of  
P388 tumor cells was in  
the range of -45 to  
+70% over the dose  
range of 0.13 to 0.006  
mg/kg.

**FIG. 11W**



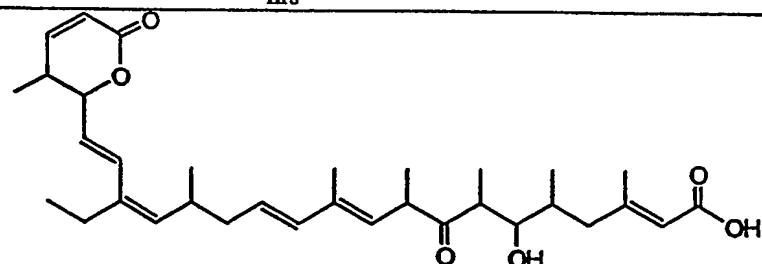
**Didemnin B/**  
*Trididemnum solidum/*  
 NSC-2325319; IND  
 24505

77327-05-0;  
 77327-04-9;  
 77327-06-1/  
 other related  
 natural  
 products

non-Hodgkin's  
 lymphoma, breast,  
 carcinoma, CNS, colon/  
 Discontinued due to  
 cardiotoxicity; nausea,  
 neuro-muscular toxicity  
 and vomiting MTD 6.3  
 mg/Kg; toxicity  
 prevented achieving a  
 clinically signif. effect;  
 rapidly cleared (t<sub>1/2</sub> 4.8  
 hrs

inhibits  
 protein  
 synthesis via  
 EF-1

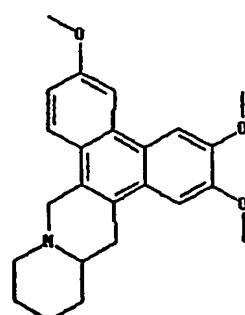
NCI 60-tumor panel  
 (GI50's): 100 nM to 50  
 fM.  
 Not potent against  
 MDR cell lines.



**Leptomyces B/**  
*Streptomyces* sp. strain  
 ATS 1287/  
 NSC-364372; elactocin

87081-35-4

NCI 60-tumor panel  
 (GI50's):  
 8 μM to 1 pM; (LC50):  
 250 μM to 10 nM  
 (several cell lines at 0.1  
 nM). Two testing  
 results with very  
 different potencies.



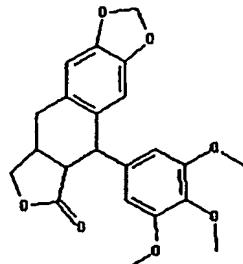
**Cryptopleurin/**

NCI 60-tumor panel

FIG. 11X

not known/  
NSC-19912

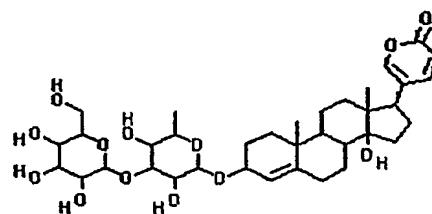
(GI50's): 19 nM to 1  
pM; (LC50): 40  $\mu$ M to  
10 nM (several cell  
lines at 1 pM).



Silicicolin/  
not known/  
NSC-403148,  
deoxypodophyllotoxin,  
desoxypodophyllotoxin  
podophyllotoxin,  
deoxysilicicolin

19186-35-7

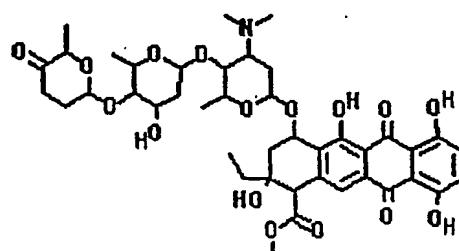
NCI 60-tumor panel  
(GI50's): ~100 nM to 3  
nM; (LC50): 50  $\mu$ M to  
10 nM



Scillaren A/  
not known/  
NSC-7525; Gluco-  
proscillarin A;  
Scillaren A

124-99-2

NCI 60-tumor panel  
(GI50's): 50 nM to 0.1  
nM;  
(LC50): 250  $\mu$ M to 0.1  
nM



Cinerubin A-HCl/  
not known/  
NSC-243022; Cinerubin  
A hydrochloride;  
CL 86-F2 HCl;  
CL-86-F2-hydrochloride

not reported

NCI 60-tumor panel  
(GI50's): 15 nM to 10  
pM; (LC50): 100  $\mu$ M  
to 6 nM

FIG. 11Y